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A Special Focus on Pediatric Research

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REVIEW ARTICLE

Bias in Epidemiological Studies: A Special Focus on Pediatric Research

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Abstract: The objective of this article is to provide an overview of bias and to discuss its impact on study results. Examples from paediatric studies are provided to acquaint the reader to different bias types.

Keywords: Bias, selection bias, information bias, confounding, children

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Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations and the application of this study to control of health problems [1]. The main purpose of epidemiological research is to collect information that will provide a basis for the prevention and control of health problems. Hence determining the causes of diseases, evaluating the magnitude of different health problems and studying the natural history of diseases are among the objectives of epidemiology. Assessing the value of new interventions either preventive or therapeutic as well as evaluating the effectiveness of public health program and policies are also in the scope of epidemiology [2].

Different types of studies are used in epidemiology. The main research question is crucial in determining the type of the study that will be conducted. While the magnitude of a health problem can be determined through a survey, evaluating the efficacy of a vaccine necessitates an experimental or a quasi-experimental design. But for all study types, the main principle is to design the methodology properly in order to yield valid research results. Any drawbacks in the design of a study threatens its validity, the degree a study appropriately measures what it intends to measure, and leads to misleading conclusions [3]. Hence when carrying out epidemiological research, it is essential to design the methodology properly in order to obtain reliable estimates. Similarly while reading an epidemiological research; it is important to evaluate the methodology thoroughly before interpreting and applying its results to clinical practice.

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Any trend in the collection, analysis, interpretation, publication or review of data that can lead to conclusions which are systematically different from the truth is called bias [1]. Since bias distorts the results of the study in a particular direction, it is also called as systematic error [4]. Bias might lead to both under and overestimation of the rate of a disease/ health condition. It can also distort the association between an exposure and an outcome. Due to bias, the researcher might not be able to detect a real association between an exposure and an outcome or conversely find an association which actually does not exist. Mainly two types of bias are described in the literature: selection and information bias. While some authors also categorize confounding as a type of bias, others refer it a separate issue. The objective of this article is to provide an overview of bias as well as to discuss its impact on study results. Examples from paediatric studies are provided to acquaint the reader to different bias types.

An error in choosing the individuals or groups to take part in a study is defined as *selection bias*. Referral filter bias is a kind of selection bias which is due to selecting the study population from the hospital or clinics. Participants drawn from clinical sources might not be representative of all the cases who have the disease. Cases that experience mild symptoms as well as the ones with a low accessibility of medical services will not be represented in a study sample drawn from clinical services. Moreover cases selected from a tertiary care hospital will not be representative of all the cases under clinical care, since the bulk of patients who have common disorders are not referred to teaching hospitals [5]. Ellenberg and Nelson provided an example of referral bias in their article through reviewing studies that evaluated the susceptibility of children with febrile seizures to later spontaneous non febrile seizures [6]. The authors determined that population and clinic based studies yielded different results regarding the occurrence of non febrile seizures among children who had experienced febrile seizures. Population based and clinic based studies differed regarding their sample selection procedures. In population based studies all children in a clearly defined population were followed up, while clinic based studies captured only the ones who were presented with febrile seizures at hospital emergency rooms or specialty clinics. The authors demonstrated that the reported percentage of children experiencing non febrile seizures after febrile seizures in population based and clinic based studies were 1.5% to 4.6% and 2.6% to 76.9%, respectively (Figure 1). The authors noted that children who had severe febrile seizures were more likely to be referred to a specialty seizure clinic, while those with pure febrile seizures more often received services from primary care. The variation in the sample selection was the main reason for the disparity of the results [6].

The sample selected from the hospital or clinics might also yield Berkson's bias, which is a kind of selection bias observed in case-control studies. If participants who have two particular diseases have a considerably higher rate of hospitalization compared to the ones who have only one of the diseases, the study might reveal an association between the two diseases even if there is no such an association in the population [5]. For instance a study carried out in a clinical sample might indicate an association between childhood migraine and learning difficulties. This finding might indicate a real association, but it also might be spurious. If the chance of referring children who have both migraine and learning difficulties to medical care is much higher than the ones who have only one of the diseases, a spurious association might be determined between the two conditions [7].

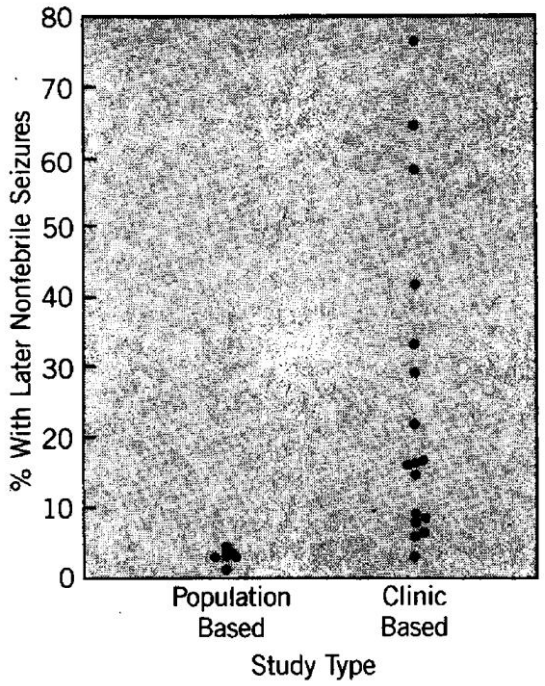

Figure 1. The rate of children who had non febrile seizures after one or more febrile seizures in population and clinic based studies (Reprinted with permission from JAMA. Ellenberg JH, Nelson KB. Sample selection and the natural history of disease. Studies of febrile seizures. JAMA. 1980;243:1337-40 [6]. Copyright ©1980, American Medical Association. All rights reserved).

The above two examples represented selection bias in hospital settings. Yet population based studies are also subject to selection bias. Non response bias occurs when the study population differs significantly from the non participants. This type of bias can distort the estimation of a health condition. Suppose a school based cross-sectional study to determine the prevalence rate of parasomnias among schoolchildren. The parents of children having parasomnias might be more interested in participating in such a study compared to the ones who do not experience such problems. The main motivation of such parents in participating might be the need to receive medical attention or to explore further the problems of their children. In that case, the prevalence determined will be an overestimation due to the non participating subjects who are free of parasomnias. Yet non response bias might result with underestimation of a health problem. Let us suppose that the above mentioned study uses a self administered questionnaire to be filled by the parents. The parents of children from lower socioeconomic status might have difficulties in filling out or returning the questionnaire and might be underrepresented in the study. This might pose a distortion on the results if children with low socioeconomic status experience higher rates of parasomnias compared to the ones in higher status. In such a case, the prevalence determined will be an underestimation, due to the low response rate among children who are socio economically disadvantaged.

Nilsen et al. demonstrated how selection bias affected the validity of study results in a large observational study [8]. The authors documented the differences in prevalence estimates between the Norwegian Mother and Child Cohort Study and all women giving birth in Norway. The Norwegian Mother and Child Cohort Study captured 73 579 women. While the sample size was large, this was only 43.5% of the invited population. The authors determined that a number of exposures and outcome variables were biased in this cohort. They indicated that woman younger than 25 years, those living alone, mothers with more than two previous births and with previous stillbirths, smokers, women with stillbirths and neonatal death were underrepresented while multivitamin and folic acid supplement users were overrepresented in this cohort [8].

Loses to follow up in a cohort and drop outs in an experimental study might also introduce

selection bias. The rate of the outcome might differ systematically between the participants who remain in the study and the ones who drop out. A study carried out by Castro et al. evaluated the possible bias that was introduced by losses in follow ups among a cohort of extremely low birth weight (ELBW) survivors (401–1000 g at birth) [9]. The authors predicted the mental development and psychomotor development of the ELBW survivors who were lost to follow up and concluded that the ones who were compliant with follow-up evaluations might have had worse mental development scores compared to the ones who were lost to follow up. The researchers noted that follow-up studies based on infants who are compliant with follow-up care might lead to an overestimation of adverse outcomes in ELBW survivors. The authors proposed that parents of infants at lower risk for severe morbidity might perceive less need for outpatient care [9].

If non response, loses to follow up or drop outs are not negligible, the socio demographic variables of the study participants should be compared with the non respondents or the ones who are lost to follow up. The systematic differences detected between the participants and the ones who refuse to participate are important in interpreting the results of the study [5]. A better way of evaluating the impact of losses of follow up or drop outs is to use the worst case scenario. We can assume a hypothetical randomized control trial which evaluates the effectiveness of a recently developed medication on survival. In such a study, some participants from both the treatment and the control group might have been lost to follow up. In order to take into consideration the drop outs, the worst case scenario can be applied. The worst case scenario assumes that all patients allocated to the treatment group and lost to follow-up died, while all patients allocated to the control group and lost to follow-up survived [3]. If assuming a worst-case scenario does not alter the conclusions derived from study results, then loss to follow-up is not considered as a problem. Yet if the worst case scenario changes the study results, the reliability will be questioned [3]. For a good example of the application of the worst case scenario, the readers can refer to a trial determining the in vivo efficacy of amodiaquine and sulfadoxine/pyrimethamine for treating Plasmodium falciparum malaria among children conducted by Gorissen et al. [10].

Selection bias is not limited to individual studies and can also affect meta-analyses. Since different studies yield varying estimates, there is a need for meta analysis which is the statistical synthesis of results from a series of studies. Meta analysis provides an overview that incorporates a quantitative strategy for combining the results of several studies into a single pooled or summary estimate [3]. Since meta analysis brings together several studies, it yields the strongest evidence and it is often appropriate for arriving at the best single estimate of the treatment effect. Yet meta analysis is mostly limited to published literature leading to publication bias. Evidence indicates that studies reporting relatively high effect sizes have a more chance of being published compared to studies that report lower effect sizes. So any bias in the literature is likely to be reflected to meta analysis, too [11]. The only true test for documenting publication bias is to compare the findings of published and unpublished studies. Yet unpublished studies are not easily accessible, so other approaches are developed to assess the impact of potential bias in meta analysis. A meta analysis aimed to determine the efficacy of sodium cromoglycate compared to placebo in the prophylactic treatment of children with asthma [12]. The authors evaluated the double-blind, placebo-controlled randomised

trials, evaluating the effectiveness of inhaled sodium cromoglycate as maintenance therapy, among children having asthma. The authors concluded that there was not sufficient evidence to be sure about the efficacy of sodium cromoglycate over placebo. They indicated that there was an under representation of small studies with negative results introducing publication bias. So the beneficial effects of sodium cromoglycate as maintenance therapy in childhood asthma might have been overestimated in individual studies [12].

The second type of bias is referred as *information bias*. Information bias results from the drawbacks in collecting, recording, coding or processing data [5]. The misclassification is a kind of information bias which is due to inadequacy of the measurement procedures. If the sensitivity or the specificity of the measurement procedure to detect exposure or the disease is limited, then some exposed participants might be classified as non-exposed or the diseased ones as non diseased [13]. Misclassification bias is categorized as differential and non differential bias. Differential misclassification occurs when the misclassification is not similar under groups of comparison. For instance exposure can be differentially misclassified in cases and controls. In that case bias in any direction might occur; a true association might be decreased, increased, obscured or its direction might change [14]. Yet in non differential misclassification, the degree of the misclassification is the same across the groups. In such a case for binary variables, the estimate is biased toward the null value, meaning any misclassification that occurs will always reduce the difference between the groups. So if the study detects a difference between the groups, it will be less than the actually existing one [13,14].

A kind of misclassification bias which is due to memory failure is called as recall bias. Mild diseases, short hospital stays or similar incidents which do not have a large impact on the participants might be forgotten and underreported. Moreover there might be differential memory failure among the groups that are compared [5]. For instance in a case control study, cases can have a higher rate of recall concerning their past exposures compared to the control group leading to differential misclassification. Even if the exposure rate is similar among the cases and the control, due to differences in the rate of recall the cases might seem to be exposed more. This will result with a spurious association between the exposure and the outcome.

Van den Brink et al. demonstrated the impact of recall bias in studies concerning headache among children and adolescents [15]. The study population included children aged 9-16 years who had had experienced headache at least weekly. A retrospective headache questionnaire and also a prospective four week headache diary were filled by the children. The authors compared headache frequency, intensity, and duration, as scored on the questionnaire and the diary. It was determined that headache intensity and headache duration were overestimated on the questionnaire compared with the diary. Also other variables influenced the rate of recall. The authors reported that age, depression, and headache severity influenced the way children and adolescents recalled their headaches. While answering the questionnaire, older children underestimated their headache frequency more than younger children did. Depressive children underestimated the number of headache complaints on a questionnaire more than their non depressive ones [15]. So the rate of recall varied between the groups which would lead to differential misclassification in retrospective studies.

Data collection through even basic clinical assessments might yield information bias. A

study carried out by Rifas-Shiman et al. demonstrated that clinical measurements of length in children younger than two years might be biased [16]. The authors compared the length measured by the clinical paper-and-pencil method with the research standard recumbent length-board method among 160 children who were younger than two years. The authors concluded that the conventional paper-and-pencil method systematically overestimated length. The mean±sd difference between clinical and the research measurements were 1.3±1.5 cm. The authors underlined the fact that paper-and-pencil measurement underestimated overweight and overestimated underweight leading to wrong estimates in the population [16].

Other types of information bias can also distort the research results. For instance in a survey conducted through face to face interviews with adolescents, some participants might not report their smoking or alcohol use correctly. Some might have a trend to underreport since smoking and alcohol use are socially undesirable behaviours. Yet some might over report, if they perceive that smoking makes them to be seen as "more grown up". The gender, age, educational level or the profession of the interviewer can alter the answers to the questions asked during the interview. The place where the interview takes place also changes the answers given; the interviews conducted at hospitals or at the community might yield different answers. The participants might be willing to provide more socially desirable answers to doctors compared to lay interviewers [5].

Contamination bias is a special type of bias which occurs in quasi experimental designs. Suppose an intervention study which evaluates the success of a school health program on increasing the physical activity of the adolescents. In such a study, the researchers might select two schools; one as the intervention and the other as the control group. Initially the baseline physical activity levels for both groups will be determined. Then the planned program will be carried out in the intervention group while no intervention will take place in the control. After implementing the program, the physical activity of both groups will be evaluated. If the intervention is effective, there will be a change in physical activity levels in the intervention group while no change or a minimal change will be detected in the control group. Yet contamination bias might distort the findings of such a study. If the intervention and the control schools are in the same neighbourhood or in close proximity, the pupils in both groups might interact. In such a case, the students in the intervention group might influence the control group in terms of their knowledge, attitude, and behaviours and enable them to increase their physical activity. Consequently this will lead to a bias toward the null hypothesis. In other words due to the contamination of the control subjects with the intervention group, the effectiveness of the intervention can be detected smaller than the actual effect [5].

Although some authors categorize *confounding* as the third type of bias, it has different attributes then the biases explained above. When an association of an exposure and a disease evaluated, a third factor which is called a confounder might distort the association. Confounder should be a known risk factor for the disease; it should also be associated with the exposure but should not be a result of the exposure [2]. For instance a study might evaluate the association between maternal smoking and hyperactivity among children [17]. While assessing such an association, maternal alcohol use might act as a confounder. Maternal alcohol use might cause hyperactivity in children, and also the rate of alcohol use might be differently distributed among the smoker and non smoker mothers. Smokers might use alcohol in a

higher rate compared to non smokers. Hence the association between maternal smoking and hyperactivity in children might be confounded by maternal alcohol use (Figure 2). Is the real association between smoking and hyperactivity or alcohol use and hyperactivity? So the researcher should determine the independent association of smoking and alcohol use with hyperactivity through controlling confounding. In randomized controlled trails, randomization can be used for controlling confounding. Matching, stratification, standardization and multivariate analysis are other methods for controlling confounding.

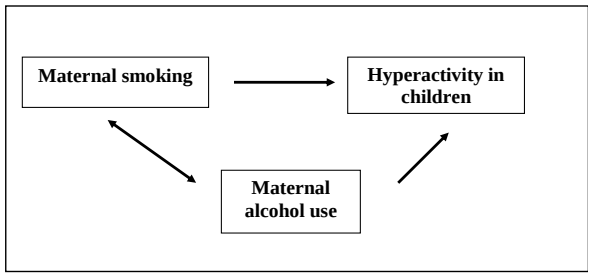

Figure 2. The schematic representation of a potential confounder, maternal alcohol use, in evaluating the association of maternal smoking and hyperactivity among children.

While designing an epidemiological study it is important to be aware of potential biases. In order to determine the rates accurately and to document causal associations, it is important to eliminate or at least minimize the biases. In most studies, it is not possible to eliminate the bias fully. In such a case, it is essential to discuss how the potential biases might have affected the study and to consider the impact of bias on the results.

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